National Institutes of Health
National Center for Complementary and Alternative Medicine (NCCAM)
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St. John's Wort

St. John's wort (*Hypericum perforatum*) is a long-living, wild-growing herb with yellow flowers that has been used for centuries to treat mental disorders as well as nerve pain. In ancient times, doctors and herbalists (herb specialists) wrote about its use as a sedative and antimalarial agent as well as a balm for wounds, burns, and insect bites. Today, the herb is a popular treatment for mild to moderate depression; it also is used to treat anxiety, seasonal affective disorder, and sleep disorders.[1]

St. John's wort is most widely used in Germany, where doctors prescribed almost 66 million daily doses in 1994 for psychological complaints.[2] In fact, German doctors prescribe St. John's wort about 20 times more often than Prozac, one of the most widely prescribed antidepressants in the United States.[3]

The use of St. John's wort is growing in the United States, and several brands now are available. Extracts of the plant are sold as a nutritional supplement after being prepared with a powder or an oil; the herb is available in capsule, tea, or tincture forms. St. John's wort was among the top-selling botanical products in the United States in 1997, with industry-estimated sales of $400 million in 1998.[4]

FDA's Role

St. John's wort is 1 of 200 plant products approved by the U.S. Food and Drug Administration (FDA) for sale to the public as a dietary supplement. The FDA does not subject dietary supplements to an extensive premarket approval process, however, as it does new drugs.[5] On the other hand, the Dietary Supplement Health and Education Act of 1994 permits the FDA to remove a supplement from the market if it determines the supplement is unsafe. Herbal products such as St. John's wort can be marketed without stating standards for dosage or evidence of safety. Often, information on specific products may be misleading or even inaccurate. For instance, when the *Los Angeles Times*, a newspaper in California, commissioned laboratory tests on 10 St. John's wort products, researchers found that the potency of the products varied dramatically from what their labels claimed.[6]

At the same time, a St. John's wort product stating the words "standardized extract" in its label may be more likely to contain the exact amount of the specific active ingredient needed to be effective. Standardized products generally are considered the highest-quality herbal products that a consumer can buy.[7]

Treating Depression

Depression is a common illness that strikes perhaps 1 in 15 Americans each year. A person's mood, thoughts, physical health, and behavior all may be affected. Symptoms can include a persistent sad, anxious, or "empty" feeling; loss of energy, appetite, or sexual drive; and lack of interest in socializing, work, or hobbies.

Depression can be mild, moderate, or severe. Mild depression is characterized by difficulty in functioning normally, while moderate depression may involve impaired functioning at work or in social activities. Severe depression, which may involve delusions or hallucinations, markedly interferes with a person's ability to work or otherwise function and may lead to suicide. Genetic factors may put a person at risk for developing depression, and alcohol or drug use can make the problem worse.[8] While the public misperception persists that

depression is voluntary or a "character flaw," depression is a real condition that can be treated effectively by qualified professionals.[9]

Specific psychotherapies (such as interpersonal and cognitive-behavioral therapy) and antidepressant medications both have been found to be effective for patients with major depression. Major depression includes mild, moderate, or severe depression that is not characterized by manic-depressive mood swings or induced by a substance such as alcohol. Several antidepressant drugs have become more widely used in the past several years and been found to be effective. However, patients sometimes report unpleasant side effects such as a dry mouth, nausea, headache, diarrhea, or impaired sexual function or sleep.[10]

In part because of these types of drug side effects, many patients with depression are turning to herbal treatments such as St. John's wort. Researchers are studying it for possibly having fewer and less severe side effects than antidepressant drugs. St. John's wort also costs far less than antidepressant medication. In addition, St. John's wort does not require a prescription.[11]

St. John's wort is not completely free of side effects, however. Some users have complained of a dry mouth, dizziness, gastrointestinal symptoms, increased sensitivity to sunlight, and fatigue.[12] In addition, herbal treatments often are not as potent or as quick to act as conventional treatments. Furthermore, herbal treatments may not produce the desired results and may not be as effective as conventional medicine. Still, some people turn to herbs because they prefer to use "natural" products.

Clinical depression is a serious medical disorder that, in many cases, can be treated. However, St. John's wort is not a proven therapy for clinical depression. Therefore, there is some risk in taking it to treat clinical depression.[5]

In any case, St. John's wort should not be mixed with other standard antidepressants because side effects may result. This is one reason why it is important to tell your doctor about all medications you are taking. Check with your doctor before taking St. John's wort or any other herb or medication. Your doctor can help you weigh the risks and benefits of a particular treatment so you can make informed health care decisions.

How St. John's Wort Works

The major components in extracts of St. John's wort include flavonoids, kaempferol, luteolin, biapigenin, hyperforin, polycyclic phenols, hypericin, and pseudohypericin. Researchers believe the last three substances are the active ingredients.[5] New research suggests that hyperforin also may play a large role in the herb's antidepressant effects. Some German manufacturers of St. John's wort have begun standardizing, not only to hypericin as most U.S. manufacturers do, but to hyperforin as well.[13] Standardizing means that the manufacturer ensures that each individual supplement contains a uniform amount of a certain compound, in this case hypericin and hyperforin.

Recent research suggests a possible application of St. John's wort for alcoholism. Researchers from the University of North Carolina at Chapel Hill found that St. John's wort reduced alcohol intake in laboratory animals.[14]

Several mechanisms of action of St. John's wort have been proposed, including the following:

- **Inhibition of monoamine (serotonin, dopamine, and norepinephrine) re-uptake:** St. John's wort appears to reduce the rate at which brain cells reabsorb serotonin (an important neurotransmitter or chemical that aids communication between nerve cells). Low levels of serotonin in the body are associated with depression.[15,16]
- **Modulation of interleukin-6 (IL-6) activity:** Raised levels of IL-6, a protein involved in the communication between cells in the body's immune (disease-fighting) system, may lead to increases in adrenal regulatory hormones,

a hallmark of depression. St. John's wort may reduce levels of IL-6, and thus help treat depression.[17]

More research is needed to determine precisely the active ingredients in St. John's wort and to learn how the herb works.

Clinical Trials

Clinical trials (studies of a treatment's safety and effectiveness in humans) have found a similar rate of response with St. John's wort as with standard, conventional antidepressants in treating mild to moderate depression.[18,19] However, it is hard to interpret these studies as definite proof of the efficacy of St. John's wort because low doses of standard antidepressants were used and there was no placebo (a pharmacologically inactive substance) control. An analysis of 23 European clinical studies of St. John's wort that was published in the *British Medical Journal* in 1996 concluded that the herb has antidepressive effects in cases of mild to moderate depression (the dosage varied considerably among the studies).[2] However, no studies of its long-term use have been conducted. More research is needed to explore the long-term effects and optimum safe dosage of the extract.

A new study funded by the National Institutes of Health's National Center for Complementary and Alternative Medicine (NCCAM), Office of Dietary Supplements, and the National Institute of Mental Health will provide more information about St. John's wort. This study, which is in progress, is the first large-scale controlled clinical trial in the United States to assess whether the herb has a significant therapeutic effect in patients with clinical depression.

The $4.3 million study involves 336 patients with major depression. The Duke University Medical Center in Durham, North Carolina, is coordinating the 3-year study, which has 12 clinical sites around the country.

There are three different treatment groups in the trial. One group will receive an initial dose of 900 mg per day of St. John's wort; a second will receive a placebo; and the third will receive Zoloft (a commonly used antidepressant). Patients who respond positively to their randomly assigned treatment will be continued on it for another 4 months.

For More Information

For more information about depression, contact the National Institute of Mental Health toll-free at 1-800-421-4211. For more information about St. John's wort, contact the American Botanical Council at 512-926-4900 or the Herb Research Foundation at 303-449-2265. For more information about complementary and alternative medicine, contact the NCCAM Clearinghouse at 1-888-644-6226.

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Results from a study conducted by the National Institutes of Health (NIH) Clinical Center alert the public to concerns about interactions between St. John's wort and Crixivan (indinavir), a protease inhibitor, and perhaps other protease inhibitors used in the treatment of HIV. Adverse reactions also have been reported with cyclosporine, a drug used to reduce the risk of organ transplant rejection. St. John's wort also may interact with other immunosuppressant drugs. Currently, data are available only for the combined use of indinavir and St. John's wort. Doctors and patients should be aware of these possible negative drug interactions that could interfere with the functioning of these drugs. For more information, please refer to an NIH News Release on NCCAM's Web site <http://nccam.nih.gov/nccam/ne/press-releases/021000.htm> or the Food and Drug Administration (FDA) Center for Drug Evaluation and Research's Web site <http://www.fda.gov/cder/drug/advisory/stjwort.htm>; or call the FDA Center for Food Safety and Applied Nutrition at 1-800-332-4010.

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